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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,555	02/20/2002	Michael Cappello	OCR-1001.US	2094
7590 03/05/2004				
Carmody & Torrance LLP 50 Leavenworth Street P.O. Box 1110 Waterbury, CT 06721-1110			EXAMINER KAM, CHIH MIN	
			ART UNIT 1653	PAPER NUMBER

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/937,555	Applicant(s) CAPPELLO ET AL.	
	Examiner Chih-Min Kam	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 December 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 6-9, 11-19 and 21-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 6, 8, 9, 11-19 and 21-30 is/are rejected.
- 7) ☒ Claim(s) 7 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Claims

1. Claims 1-4, 6-9, 11-19 and 21-30 are pending.

Applicants' amendment filed December 18, 2003 is acknowledged, and applicants' response has been fully considered. Claims 1-4, 8, 9, and 11-19 have been amended, claims 5 and 10 have been cancelled, and new claims 21-30 have been added. Thus, claims 1-4, 6-9, 11-19 and 21-30 are examined.

Oath/Declaration

2. The supplemental declaration filed December 18, 2003 is acknowledged.

Objection Withdrawn

3. The previous objection to the disclosure regarding embedded hyperlink, is withdrawn in view of applicants' amendment to the specification in the amendment filed December 18, 2003.

Rejection Withdrawn

Claim Rejections - 35 USC § 112

4. The previous rejection of claims 1-11 and 14-16 under 35 U.S.C. 112, second paragraph, regarding the term "at least about", "GPIIb/IIIa", "GPIa/IIa" or "ADP", is withdrawn in view of applicants' amendment to the claim, applicants' cancellation of the claim, and applicant's response at page 10 of the amendment filed December 18, 2003.

Claim Objections

5. Claim 2 is objected to because of the use of the term "A polypeptide according claim 1". Since claim 2 is dependent from claim 1, the term "The polypeptide according claim 1" should be used. See also claims 3-4, 6-7, 13-16, 21-24, 26-27, 29 and 30.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 6, 8, 9, 11-19, 21-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide of SEQ ID NO:2, does not reasonably provide enablement for a purified polypeptide being a fragment or variant of SEQ ID NO:2 having at least 95% sequence homology to the naturally occurring polypeptide and having activity of inhibiting platelet function, a pharmaceutical composition comprising an effective amount of the polypeptide, or a method of treating a patient using the polypeptide; a purified polypeptide isolated or cloned from a hookworm having molecular weight of 15-25 kDa and the activity of interfering with the binding of cell surface integrin to its ligand, a pharmaceutical composition comprising the polypeptide, or a method for treating a patient by administering the polypeptide, where the sequence of the polypeptide and the disease is not identified; or a purified polypeptide comprising residues 1-40 of SEQ ID NO:2, or a fragment or variant thereof having at least 95% sequence homology to the naturally occurring polypeptide, where the parent polypeptide or the function of the polypeptide are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-4, 6, 8, 9, 11-19, 21-30 are directed to a purified polypeptide of SEQ ID NO:2 or a fragment or variant of thereof having at least 95% sequence homology to the naturally occurring polypeptide and having activity of inhibiting platelet function (claims 1-4, 6, 21 and

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22); a pharmaceutical composition comprising an effective amount of the polypeptide (claims 8 and 11), or a method of treating a patient using the polypeptide (claim 9); a purified polypeptide isolated or cloned from a hookworm having molecular weight of 15-25 kDa and the activity of interfering with the binding of cell surface integrin to its ligand (claims 12-16, 23 and 24), a composition or pharmaceutical composition comprising the polypeptide (claims 17 and 19), or a method for treating a patient by administering a hookworm polypeptide (claim 18); or a purified polypeptide comprising residues 1-40 of SEQ ID NO:2, or a fragment or variant thereof having at least 95% sequence homology to the naturally occurring polypeptide (claims 25-30). The specification, however, only discloses cursory conclusions (pages 3-4) without data supporting the findings, which state that a polypeptide is isolated and purified from *Ancylostoma caninum* hookworms, and then cloned, this polypeptide (SEQ ID NO:2) inhibits platelet aggregation and adhesion in response to various agonists by interfering with the binding of at least one cell surface integrin; the invention also provides fragments or variants of the polypeptide exhibiting at least 50% sequence homology to the naturally occurring polypeptide, which exhibit the same biological properties as the native compound; and methods of using these polypeptides in the treatment of diseases. There are no indicia that the present application enables the full scope in view of polypeptides obtained from hookworms and their use in the treatment of diseases as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence of working examples, the state of the prior

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art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the fragment or variant of SEQ ID NO:2, the polypeptide obtained from hookworms, the treating conditions for diseases using the polypeptide, and the variant or fragment of a polypeptide comprising residues 1-40 of SEQ ID NO:2, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification indicates an extract and an excretory/secretory product (ES) of *Ancylostoma caninum*, and a hookworm platelet Inhibitor (HPI), SEQ ID NO: 2 inhibit platelet aggregation and adhesion, especially inhibition of fibrinogen binding to GP IIb/IIIa or inhibition of collagen binding to GPIa/IIa by HPI (Examples, pages 11 -23). However, there are no other working examples indicating the claimed variants or the methods in association with the variants.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Pritchard *et al.*, WO 95/12615; Furmidge, *Parasitology* 112, 81-87 (1995)) teaches the excretory/secretory (ES) products from the human hookworm *Necator americanus* inhibit the activity of Factor Xa and platelet aggregation. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on identities of fragments or variants of SEQ ID NO:2, the polypeptide comprising residues 1-40 of SEQ ID NO:2 or its fragments or variants,

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the hookworm peptides, and the treating conditions for various integrin related diseases using the polypeptide and the effect of the polypeptide to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass many peptide variants, the treating conditions such as the dose of the peptides used and the effects of the peptides in the treatment of diseases are not described in the specification, the invention is highly unpredictable regarding the amino acid sequence of the hookworm peptide and the outcome of the treatment using the hookworm peptide.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to hookworm polypeptides; a composition comprising an effective amount of the hookworm polypeptide for in vivo treatment; or a method for treating a patient by administering the polypeptide. The specification indicates an extract and an excretory/secretory product (ES) of *Ancylostoma caninum*, and a hookworm platelet Inhibitor (HPI), SEQ ID NO: 2 inhibit platelet aggregation and adhesion (Examples, pages 11 -23), and one hookworm polypeptide has been identified as SEQ ID NO:2. However, the specification has not identified any variant or fragment of SEQ ID NO:2, a polypeptide comprising residues 1-40 of SEQ ID NO:2, or other hookworm polypeptides having the activity of interfering with the binding of cell surface integrin to its ligand and a molecular weight of 15-25 kDa than SEQ ID NO:2, nor has demonstrated the use of a hookworm polypeptide or its fragment or variant in the treatment of diseases. There are no working examples indicating the sequence identities of various hookworm polypeptides except SEQ ID NO:2 and the treating conditions for various diseases using the hookworm polypeptide. Furthermore, there is no *in vivo* data demonstrating

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the hookworm polypeptide is effective in inhibiting platelet function, inducing immune response or treating an identified disease in patient, nor indicating how to extrapolate the in vitro data to in vivo effect. Therefore, it is necessary to have additional guidance on the identities of various hookworm polypeptides, and the treating conditions such as dose and time for diseases using the hookworm polypeptide, and to carry out further experimentation to assess the in vivo effect of the hookworm peptides having activity of inhibiting platelet function.

(6). Nature of the Invention

The scope of the claims includes many structural variants, however the specification has not demonstrated the use and the effects of these peptide variants in the treatment of diseases. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants, and the teaching in the specification is limited, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of the claimed invention.

In response, applicants indicate claim 1 has been amended to recite the polypeptide of SEQ ID NO:2, or its fragment or variant having at least 95% sequence homology to the naturally occurring polypeptide and having activity of inhibiting platelet function, and Example 14 of USPTO training materials in written description indicates procedures of making variants of the identified sequence having 95% identity to the listed sequence and retaining its activity are conventional in the art; claims 8, 9, 17 and 18 have also been amended to state the composition is used to inhibit platelet aggregation and platelet adhesion, and to define the composition as including an effective amount of the polypeptide mixed with a carrier and other optional

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ingredient; and claim 12 has been amended to recite the polypeptide that interferes with the binding of cell surface integrin to its ligand, and has a molecular weight of 15-25 kD (pages 8-10 of the response). The response has been fully considered, however, the argument is not persuasive because the specification only demonstrates SEQ ID NO: 2 inhibits platelet aggregation and adhesion, it has not identified any variant or fragment of SEQ ID NO:2 or a hookworm polypeptide, which encompassed by the claims. Furthermore, the specification does not provide sufficient teachings on the use and the in vivo effects of various hookworm peptides including the fragments or variants thereof in the treatment of diseases, thus the full scope of the claims is not enabled as indicated in the section above. As to Example 14 in the written description training material, the example merely indicates the procedures of making the variants of the identified sequence having 95% identity to the listed sequence and retaining its activity are conventional in the art. The specification still needs to provide sufficient teachings on structure to function/activity of the polypeptides and the representative species for the variant or fragment of the polypeptide because without the guidance, one skilled in the art would not know which region or residue(s) of the polypeptide is essential for function/activity, and how to identify a functional peptide.

7. Claims 1-4, 6, 8, 9, 11-19, 21-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 6, 8, 9, 11-19, 21-30 are directed to a purified polypeptide of SEQ ID NO:2 or a fragment or variant of thereof having at least 95% sequence homology to the naturally

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occurring polypeptide and having activity of inhibiting platelet function (claims 1-4, 6, 21 and 22); a pharmaceutical composition comprising an effective amount of the polypeptide (claims 8 and 11), or a method of treating a patient using the polypeptide (claim 9); a purified polypeptide isolated or cloned from a hookworm, which interferes with the binding of cell surface integrin to its ligand, and the polypeptide has a molecular weight of 15-25 kD (claims 12-16); a composition or a pharmaceutical composition comprising an effective amount of the polypeptide (claims 17 and 19); or a method for treating a patient by administering the polypeptide (claim 18); a purified polypeptide comprising residues 1-40 of SEQ ID NO:2, or a fragment or variant thereof having at least 95% sequence homology to the naturally occurring polypeptide (claims 25-30). The specification indicates that a polypeptide is isolated and purified from *Ancylostoma caninum* hookworms, and then cloned, this polypeptide (SEQ ID NO:2) inhibits platelet aggregation and adhesion in response to various agonists by interfering with the binding of at least one cell surface integrin; fragments or variants of the polypeptide having at least 50% sequence homology to the naturally occurring polypeptide exhibit the same biological properties as the native polypeptide; methods of using these polypeptides in the treatment (page 3, line 16-page 4, line 2); and an N-terminal amino acid residues 1-40 of SEQ ID NO:2 (page 22, lines 12-22). However, the specification has not identified any variant or fragment of SEQ ID NO:2, any polypeptide isolated or cloned from a hookworm and having MW of 15-25 kDa aside from SEQ ID NO:2, nor has demonstrated using a composition comprising the polypeptide to treat a patient with an identified disease. Furthermore, the specification has not identified a specific variant or fragment of a polypeptide comprising residues 1-40 of SEQ ID NO:2 having at least 95% sequence homology to the naturally occurring polypeptide. There are no examples indicating the

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polypeptides isolated or cloned from hookworms having MW of 15-25 kDa, or the variant or fragment of SEQ ID NO:2 or a polypeptide comprising residues 1-40 of SEQ ID NO:2 having at least 95% sequence homology to the naturally occurring polypeptide are functional except for SEQ ID NO:2, and the use of these polypeptides in the treatment of platelet related diseases.

Without guidance on structure to function/activity of the hookworm polypeptide and the treating conditions for various diseases using the polypeptide, one skilled in the art would not know which region or residue(s) of the polypeptide is essential for function/activity, how to identify a functional peptide, and how to use the polypeptide in the treatment of diseases. The lack of a structure to function/activity relationship and the lack of representative species for the hookworm polypeptides and their use in the treatment of diseases as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 8, 9, 17, 18 and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claim 8 is indefinite as to what effective amount of the polypeptide would do. See also claim 17. The term “for inhibiting at least one of platelet aggregation and platelet adhesion in patient” is an intended use, which does not play weight in the claimed composition, thus it can be

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deleted. Addition of the term “wherein the amount of polypeptide is effective to inhibit at least one of platelet aggregation and platelet adhesion in patient” at the end of claim is suggested.

10. Claims 9 and 18 are indefinite because the claim recites a method for treating a patient however, it does not identify what condition or disease being treated using the claimed polypeptide. Claims 9 and 18 are also indefinite as to “unacceptable toxicity”, it is not clear what toxicity is referred to.

11. Claims 25-30 are indefinite because of the use of the term “a fragment or variant thereof”. The term “a fragment or variant thereof” renders the claim indefinite, it is not clear what parent peptide is referred to for the fragment or variant, e.g., is it SEQ ID NO:2, residues 1-40 of SEQ ID NO:2, or the polypeptide comprising residues 1-40 of SEQ ID NO:2? Claims 26, 27, 29 or 30 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

12. Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

13. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. *CMK*
Patent Examiner

Christopher S. F. Low
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SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1800

February 27, 2004